**Remarks**

Prior to this response claims 1-2, 5, 8-11, 13-15, 17, 30 and 32 were pending in the application. Claims 25-29 had been withdrawn. In this response, claims 3-7, 12, 16, 17 and 32 have been cancelled. Although claims 18-24 and 31 have been withdrawn by the Examiner in the Office Action of April 26, 2007, Applicant submits that, following the amendment of claim 1, claims 18-24 and 31 can now be rejoined as falling under allowable generic claim 1. Therefore, claims 1-2, 8-11, 13-15, 18-24, 30 and 31 are now pending in the application. No new matter has been added.

In response to the office action of September 5, 2006, Applicant had elected the *UGT1A9* gene and elected *with traverse* the T-275A substitution. This is the subject matter which is pending in the current set of amended claims. The Applicant reiterates its intention to request a rejoinder of subject-matter of claim 31 when the subject-matter of claim 1 is deemed allowable.

**Arguments**

The Examiner starts the office action by stating that claims 1, 2, 5, 8-11, 13-15, 17, 30 and 32 are rejected under 35 U.S.C. § 112 first paragraph because they lack proper written description. Particularly, the Examiner states that the claims do not define the nucleotide variation in terms of particular structure or function and that the specification does not disclose and fully characterize the genus required by the claims of any variation in the *UGT1A9* gene. Applicant fails to understand why the Examiner applies this rejection to claim 17. However, and strictly in order to advance prosecution of the current patent application, claim 1 has been amended to recite:

*"...said variation comprising a* $T^{275}A$ *substitution; ...*

This amendment renders moot the rejection under written description requirement.

Applicant reserves the right to pursue the deleted subject matter in a separate patent application.

On page 7 of the office action, the Examiner rejects claims 1-2, 5, 8-11, 13-15, 17, 30 and 32 under 35 U.S.C. § 112 first paragraph because the specification does not reasonably provide enablement for a method of the scope of the claims. Specifically, the Examiner states that claim 1 reads on any type of sample, any type of variation in glucuronidation, any biologically active compound and any polymorphic or haplotypic variation in exon 1 or the promoter of *UGT1A9*.

In order to advance prosecution of the current patent application, claim 1 has been amended to read:

*A method for determining the predisposition or susceptibility of a human individual to an adverse reaction, a side effect or a variation in response to therapy to a biologically active compound that is metabolized through UGT1A9 glucuronidation, said method comprising:*

- *obtaining a nucleic acid sample from said individual; and*
- *determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of UGT1A9 gene of said individual, said variation comprising a $T^{-275}A$ substitution;*

*whereby the presence of the polymorphic or haplotypic variation in said nucleotide sequence is indicative of said predisposition or susceptibility.*

Claim 1 as amended now reads on a nucleic acid sample (not any type of sample); a biologically active compound that is metabolized through *UGT1A9* (not any biologically active compound); and a T-275A substitution (not any polymorphic or haplotypic variation in exon 1 or the promoter of *UGT1A9* gene). With respect to the rejection of the expressions "variation in glucuronidation", this expression no longer appears in the claim, rendering this rejection moot.

The Examiner further states that because of the unpredictability of the art such as chemistry and biology, claim 1 is rejected because broadly drawn to a method for determining the predisposition of the human individual to a variation in glucuronidation activity of a biologically active compound that is metabolized through glucuronidation. Amended claim 1 is now drawn to a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, a side effect or a variation in response to therapy to a biologically active compound that is metabolized through *UGT1A9* glucuronidation. It is respectfully argued that the determination of whether or not a biologically active compound is metabolized through *UGT1A9* glucuronidation can be assessed routinely by a person skilled in the art using kits that are available commercially. A declaration to that effect from Dr. Chantal Guillemette is enclosed herewith.

*Teachings of the specification and state of the art*

The Examiner states that the specification teaches that DNA samples from Caucasian subjects were used to genotype the *UGT1A9* gene and that the specification does not teach any other type of samples. With respect, African-American subjects were also studied as stated in page 16, line 8 . In addition, types of samples are specified as "nucleic acid samples such as DNA or RNA" as stated on page 11, line 9 to 11 of the specification.

Examiner further states that the specification does not teach any additional mutations in exon 1 or the promoter region of the *UGT1A9* gene. Amended claim 1 renders this objection moot.

The Examiner further states that the graph of figure 12 shows such ovelap that it cannot be determined if these results are significant. With respect, the Examiner cannot argue with the fact that these results have been published in peer-reviewed journals (see Girard *et al.* enclosed) and that the *p* value for ANOVA oneway analysis on transformed data are shown as well as results of the Turkey-Kramer HSD test, where [alpha] value was set to 0.05 ($*p < 0.05$) indicating that such result is indeed significant.

The Examiner ends this section indicating that the specification does not teach an association between the -275 mutant allele and any other biologically active compound other than SN38. With respect, Applicant wishes to point out that Figure 12 does show an effect on MPA. In addition to those two exemplified compounds, other biologically active compounds that are metabolized through *UGT1A9* glucuronidation can be easily assessed by the person skilled in the art using commercially available kits for Human UGT1A9 Microsomes by BD Biosciences. Finally, the Examiner states that the specification does not teach an association between the -275 mutated allele and any other physiological reaction besides higher glucuronidation, once again, the amendment brought to claim 1 renders this rejection moot.

*The predictability or unpredictability of the art and degree of experimentation*

The Examiner's objection because the specification does not teach a predictable means for identifying additional variations associated with higher glucuronidation rate is rendered moot by the amendment of claim 1.

The Examiner also specifies that it is unpredictable whether the results obtained can be extrapolated to other biologically active compounds that are metabolized through glucuronidation. The Examiner states that the teaching in the specification are limited to an association between the -275 mutation and a higher glucuronidation rate with SN38. The Examiner further states that there are no teachings in the specifications regarding the -275 mutation and the glucuronidation rate of other drugs. Claim 1 as now amended, is drawn to a drug that is metabolized through *UGT1A9* glucuronidation. It is respectfully submitted that it is well within the skill of the art of the person skilled in the art to assess whether a drug is metabolized through *UGT1A9* glucuronidation with the use of commercially available kits.

*Amount of direction or guidance provided by the specification*

The Examiner objects to the fact that, to identify the different variants of the *UGT1A9* gene would require extensive experimentation. The amendment brought to claim 1 renders this objection moot.

*Working examples*

The Examiner stipulates that there are no specific examples provided in the specifications in which the -275 mutated allele was associated with any other type of physiological reaction with SN38. Applicant herewith submits 2 peer-reviewed articles that appeared since the filing of this patent application disclosing a relationship between -275 mutation and mycophenolic acid (MPA) pharmacokinetics (Kuypers *et al.* and Lévesque *et al.* enclosed).

Finally, the Examiner stipulates that there are no specific examples in which non-human organisms were used. With respect, claim 1 stipulates that the organisms is a human individual.

In conclusion, the Examiner rejects all pending claims as not being enabled without undue experimentation. Once again, the Applicant respectfully submits that claim 1 as amended, is fully enabled for a person of skill in the art.

Finally, on page 15 of the office action, the Examiner ends the office action by stating that the claims encompass detecting any variant in exon 1 or the promoter of *UGT1A9* when really, they are only enabled for detecting the T(-125)A (*sic*) variant in the promoter region of the *UGT1A9*. Claim 1 has been amended, *with traverse*, to cover only the $T^{-275}A$. Applicant

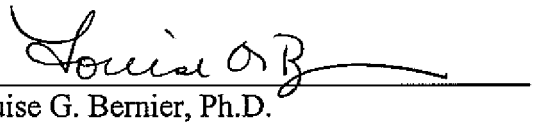
reserves its right to request a rejoinder or prosecute deleted subject-matter in separate applications. The Examiner is respectfully requested to withdraw the rejection of the claims based on lack of enablement.

It is therefore submitted that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested and allowance of claims 1-2, 8-11, 13-15, 18-24, 30 and 31 at an early date is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

A fee of 395$ is believed to be required in order to file the Request for Continued Examination for small entity status accompanying this response. Authorization is hereby given to charge account number 19-5113 with this amount. No other fees are believed to be required by the present response. However, should this be an error, authorization is hereby given to charge deposit account 19-5113 for any underpayment or to credit any overpayment.

Respectfully,



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encl: Girard *et al.*

Kuypers *et al.*

Lévesque *et al.*

Declaration of Chantal Guillemette and enclosures